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Low Molecular Weight Heparin Stimulates Megakaryocytopoiesis in Bone-Marrow Transplantation Patients

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The use of low molecular weight heparin (LMWH) as prophylaxis for veno-occlusive disease of the liver has been studied in patients undergoing bone marrow transplantation (BMT). The present study analyzes the effect of LMWH on the time course of platelet recovery after BMT. Significantly accelerated platelet recovery in conjunction with lessened requirements of platelet transfusions was observed in the LMWH-treated patients. © 1996 Wiley-Liss, Inc.

***Key words:* low molecular weight heparin, megakaryocytopoiesis, bone-marrow transplantation**

INTRODUCTION

Low molecular weight heparin (LMWH) has a greater bioavailability and longer half-life than unfractionated heparin (UH), properties that permit its administration at a lower rate than that required with UH. Enoxaparin, an LMWH, has been shown to be effective in the prophylaxis and treatment of thrombosis, with the added advantage of a lesser propensity for bleeding complications than the incidence associated with UH [1,2]. Recently, we launched a double-blind placebo-controlled feasibility and safety study of LMWH as prophylaxis for veno-occlusive disease (VOD) of the liver in patients undergoing bone-marrow transplantation (BMT) [3]. It appeared that not only did the drug fail to enhance bleeding tendency in the severely thrombocytopenic patients, it even significantly lessened the requirements for platelet transfusions. The present report elaborates on this serendipitous finding by analyzing the effect of LMWH on the time course of platelet recovery after BMT.

SUBJECTS AND METHODS

The BMT (24 allogeneic, 37 autologous) patients with malignancy in the present analysis had been enrolled in a previous study to determine the feasibility and safety of LMWH in VOD prophylaxis [3]. Patients were randomized with respect to enoxaparin (40 mg × 1/day) or placebo (saline) administration by subcutaneous injection, prior to BMT conditioning and up to 40 days post-transplantation [3].

RESULTS

Time to platelet recovery ($>20 \times 10^9$/l) was significantly shorter (16.5 ± 11.5 days vs. 29.6 ± 22.6 days; $P = 0.0075$), and platelet transfusion requirements were significantly lower (11.2 ± 8.7 units of single-donor platelets/patient vs. 17.6 ± 14.8; $P = 0.05$), in the LMWH patients compared with the placebo group.

To determine the trend of the daily mean platelet counts of the two study groups, we used an intergroup clustering technique (Fig. 1). The values were clustered per 4 days to form a single representative mean. The analysis focused on the time period between the lowest common platelet counts as induced by the conditioning effect and the end of the study. The t-test was applied for statistical evalua-

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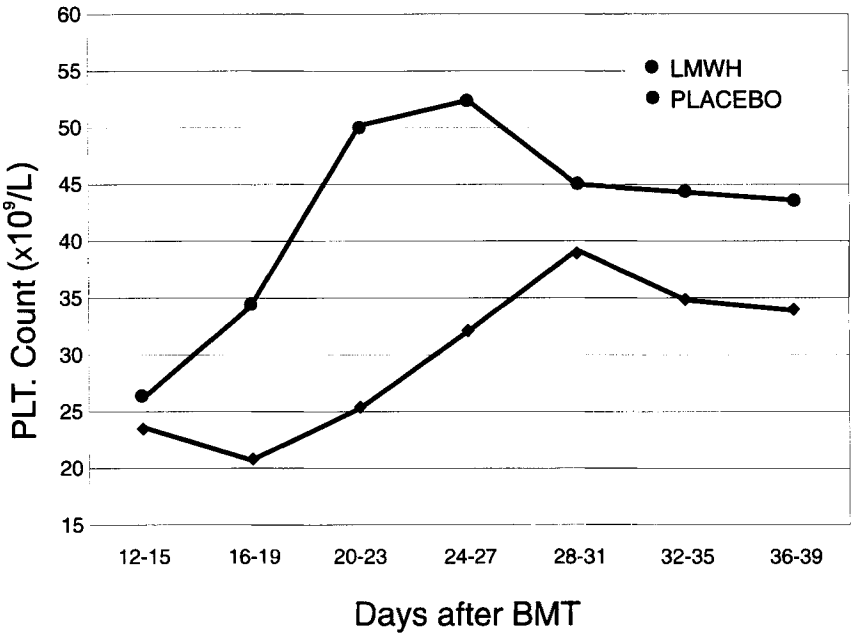

Fig. 1. Platelet recovery in post-BMT period. Values on placebo and LMWH graphs represent mean platelet count of 4-day intergroup clusters. On day +12 both groups reached pretransplant conditioning-induced lowest platelet count; day +40 signifies end of the study.

tion. The difference between the two groups was significant for days 16–19 and days 20–23 ($P = 0.005$ and $P = 0.001$, respectively), and diverged marginally for the 24–27-day period ($P = 0.056$) post-BMT.

Hemorrhagic episodes occurred significantly less frequently (2.3 ± 2.5 vs. 5.3 ± 6.5 events/patient; $P = 0.025$), and were of shorter duration (2.3 ± 2.6 vs. 5.8 ± 6.0 days/patient; $P = 0.006$) in the LMWH group than in the placebo set of patients. Thrombus formation occurred in only one patient of either group, each of whom developed a Hickman catheter-related event.

The time interval between BMT and recovery of neutrophil count ($>0.5 \times 10^9$/l) was similar for both groups. No significant differences were found between the two groups with respect to packed red blood, plasma, and cryoprecipitate requirements.

DISCUSSION

Delayed platelet reconstitution, the "Achilles' heel" of BMT, culminates in major morbidity and mortality. Since LMWH appears to be associated with a lower bleeding tendency than does UH [1], we initiated a pilot study to evaluate the effect of LMWH on VOD in thrombocytopenic BMT patients [3]. An interesting and unexpected finding of that study was the diminished platelet consumption and increased platelet production in patients treated with LMWH. In the present work we analyzed the time course of platelet recovery in the patients who had participated in that previous study, and we demonstrated that LMWH significantly shortened the time to platelet production after BMT. The accelerated platelet recovery during the first 12–28 days post-BMT, a period crucial in terms of thrombocytopenia-associated complications, indicated participation of LMWH in the stimulation of megakaryocytopoiesis. It has been demonstrated that glycosaminoglycans (GAG), including the LMWH fraxiparin, stimulate the growth of megakaryocyte colonies in vitro and in mice [4]. In vivo, its administration has induced enhanced platelet counts in these animals [5]. Very low doses of heparin administered to patients with idiopathic thrombocytopenic purpura have been shown to enhance platelet production [6]. It has been claimed that this effect of GAG is due to neutralization of megakaryocytopoiesis inhibitors, such as platelet factor 4 and transforming growth factor β [4–6], and also due to enhancement of the effect of growth factors (thrombopoietin) contained in aplastic serum [6]. Spiro et al. [7] observed high platelet counts (900×10^9/l) in hip-surgery patients who had been given LMWH as a prophylactic measure for deep-vein thrombosis. They attributed this reactive thrombocytosis to rebound overproduction as a consequence of platelet consumption during surgery, and not to a direct involvement of the drug in enhancing megakaryocytopoiesis as occurred in the BMT patients in the present study.

In summary, our results in conjunction with the data reported in the literature may provide the basis for the clinical utilization of LMWH in the treatment of various

thrombocytopenias [8]. The mechanism of action of LMWH as it affects megakaryocytopoiesis and platelet production remains to be elucidated.

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